Remarks

Submitted herewith is a Declaration of inventors Madison and Smith for the Examiner's consideration. The Declaration explains that the successful grafting of a surface loop with a specific binding characteristic into a therapeutic entity (while retaining the specific binding characteristic of the loop and the therapeutic property of the entity) was an unexpected result. The points made in the Declaration underscore the patentability of the present invention.

1. **Claims 13-24, 65, and 67 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for reciting "IgG-like."**

This rejection is respectfully traversed. The term "IgG-like" is used often in the scientific literature, demonstrating that it has an understood meaning in the art. An "IgG-like" molecule is one that possesses structural similarity to immunoglobulin domains Immunoglobulin domains are typically 90-120 amino acids in length and are comprised of two layers of beta-pleated sheets. Each beta sheet is comprised of 3-5 beta strands that run anti-parallel to one another. Each beta strand is connected by a series of protein surface loops.

For example, Champion et al. use the term in discussing key domains within the *Staph. aureus* collagen-binding surface protein. They state " B1 has two domains (D1 and D2) placed side-by-side. D1 and D2 have similar secondary structure and exhibit a unique fold that resembles but is the inverse of the immunoglobulin-like (IgG-like) domains." ("Novel fold and assembly of the repetitive B region of the *Staphylococcus aureus* collagen-binding surface protein," (*Structure 2000*, Vol. 8, No 1, pp. 67-78, Abstract). The authors further discuss D1 as an IgG-like structure in the legend to Figure 3 "The D1

resembles the IgG-like structure with the four- and three stranded barrel, but exhibits a novel fold." (p. 70). And again on page 77 (left column) in discussing B factors of proteins, the authors state "The average B factors for IgG-like domains vary between 13.0 A^2 (for fibronectin) and 50.4 A^2 (for ICAM-2)."

Furthermore, in describing a study of protein tyrosine phosphatases, Crossland et al., state "The predicted protein of ~ C160 kDa, called PTPp, comprises an extracellular portion with a MAM (meprin -- A5 antigen -- PTPμ) domain, an IgG-like domain and four Fibronectin III-like repeats..." (*Biochem. J.* (1996) 319: 249-254, Abstract).

In yet another example, Cunningham et al., describe steps in the engineering of the protein Flt-1, stating "To localize the extracellular region of Flt-1 that is involved in ligand interactions, we prepared secreted fusion proteins between various combinations of its seven extracellular IgG-like folds." (Cunningham et al., "Identification of the extracellular domains of Flt-1 that mediate ligand interactions," *Biochem Biophys Res Comm* (1997) Feb 24;231(3):596-9, Abstract).

Therefore, the term "IgG like" is commonly used and understood in the art because its meaning is commonly understood as referring to a protein that has structural similarity to immunoglobulin protein domains.

Regarding the term "flexible loop," this term is defined at page 2, line 29 et seq. of the specification, which states "Flexible loops are found on the surface of most protein modules and exist as stretches of 4-20 amino acids that connect regions of defined secondary structure."

In view of the above, both terms are appropriately defined and the person of ordinary skill in the art understands their meaning.

2. Claims 13-24, 65, and 67 are rejected under 35 U.S.C. 112, first paragraph as allegedly not enabling protein and exogenous protein surface loops which are noncovalently linked.

The rejection is believed to be inapplicable to the presently submitted claims, which recite that the therapeutic agent and the exogenous surface loop are covalently linked.

3. Claims 67 and 13-17 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Mouritsen et al. as evidenced by van Oatade et al.

This rejection is respectfully traversed. The present claims recite a therapeutic agent having a therapeutic property covalently linked to an exogenous surface loop that specifically binds to a target. The claimed therapeutic entity retains its therapeutic property after binding and the surface loop has a specific binding characteristic for the target.

Mouritsen et al. state that a T-cell epitope can be inserted into a recipient "self" protein to make the recipient "self" protein immunogenic (TNFα in Ex. 3 of Mouritsen). The T-cell epitopes described by Mouritsen do not bind to the T-cell receptor, neither as free peptides nor as a part of a protein into which they have been inserted. Indeed, Mouritsen et al explicitly describe this process at p. 2, line 35 - p. 3 line 13, where it is stated "TH lymphocytes recognize protein antigens presented on the surface of the APC (antigen presenting cells). They do not recognize, however, the native antigen per se. Instead they appear to recognize a ligand consisting of two components, a 'processed' (fragmented) protein antigen (the so-called T cell epitope) and a Major Histocompatibility Complex II". Binding to the T-cell receptor occurs only after the recipient protein is

internalized and degraded, that is after the T-cell epitope has been removed from the recipient protein. This is done by antigen processing cells and the resulting free peptide is transported and bound non-covalently to the Major Histocompatibility Complex (MHC). The MHC is a large (approximately 63 kD), two subunit transmembrane protein and not within the "4-20 amino acids" recited in the claims. It is this large, non-covalent complex of three entities that binds the T-cell receptor. Therefore, Mouritsen does not describe any therapeutic entity that has an exogenous surface loop that specifically binds to a target and the present claims are not anticipated by Mouritsen.

4. Claims 67 and 13-22 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Barbas in view of Mouritsen and van Ostade.

This rejection is respectfully traversed. As explained above, Mouritsen does not disclose or suggest a therapeutic agent having an exogenous surface loop of 4-20 amino acids that specifically binds to a target.

The present claims recite that the therapeutic agent comprises a therapeutic entity and an exogenous surface loop, and that the entity retains its therapeutic property and the surface loop retains its specific binding characteristic. Barbas discloses a Fab-9 molecule having an inserted RGD sequence. But the Fab-9 molecule of Barbas does not have a therapeutic property, as presently claimed. Even if one were to make the extraordinary assertion that the original antibody against HIV gp 120 had therapeutic activity (a claim Barbas does not make), this activity is destroyed by the manipulations performed by Barbas. Therefore, Barbas fails to teach or suggest the presently claimed invention because his approach to antibody engineering, unlike the present invention, destroys the

original activity of the antibody. Neither Barbas nor Mouritsen provide a motivation or manner of enabling the production of a therapeutic agent that retains its therapeutic property after insertion of an exogenous surface loop. Van Ostade also fails to cure these deficiencies. Reconsideration and withdrawal of the rejection is respectfully requested.

5. Claims 23, 24, and 65 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Barbas in view of Mouritsen, Van Ostade, as applied to claims 67 and 13-22, and further in view of Anderson, Goeddel, and Bode.

For the reasons described above, Barbas in view of Mouritsen and van Ostade fail to teach or suggest the presently claimed invention. Neither Anderson, Goeddel, nor Bode supplies the missing teachings described above. Therefore, the present invention is not obvious over the cited combination.

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Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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